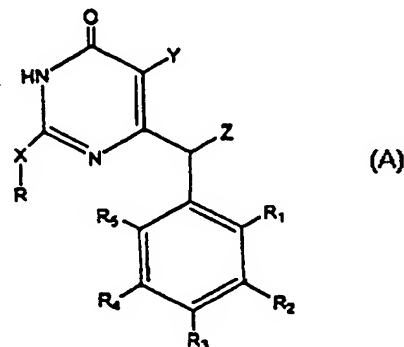




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| (51) International Patent Classification ⁷ : C07D 239/52, 239/56, 239/46, 239/36, A61K 31/505 | A1 | (11) International Publication Number: WO 00/03998 (43) International Publication Date: 27 January 2000 (27.01.00) |
| (21) International Application Number: PCT/EP99/05134 (22) International Filing Date: 19 July 1999 (19.07.99) (30) Priority Data: CA98A000015 17 July 1998 (17.07.98) IT (71) Applicant (for all designated States except US): NOVIRIO PHARMACEUTICALS LIMITED [--]; Walker Secre- taries, Walker House, Grand Cayman (KY). (72) Inventors; and (75) Inventors/Applicants (for US only): LA COLLA, Paolo [IT/IT]; 5a, Strada, 11, Poggio dei Pini, I-09012 Capoterra (IT). ARTICO, Marino [IT/IT]; Via Edgardo Negri, 64, I-00128 Roma (IT). (74) Agents: MODIANO, Guido et al.; Modiano, Josif, Pisanty & Staub, Baaderstrasse 3, D-80469 München (DE). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> |
| (54) Title: SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM | | |
| (57) Abstract The invention concerns novel substituted 6-benzyl-4-oxopyrimidines of general formula (A). These compounds inhibit reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof, and find their application in the prevention and treatment of HIV infection and the treatment of the resulting acquired immune deficiency syndrome (AIDS). Pharmaceutical compositions containing the compounds and a method of use of the present compounds and other agents for the treatment of AIDS and viral infection by HIV are also envisaged. | | |



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SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

5

The present invention is concerned with compounds which inhibit the reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof and are of value in the prevention of infection by HIV, the treatment
10 of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS). It also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS and viral infection by HIV.

15 **BACKGROUND OF THE INVENTION**

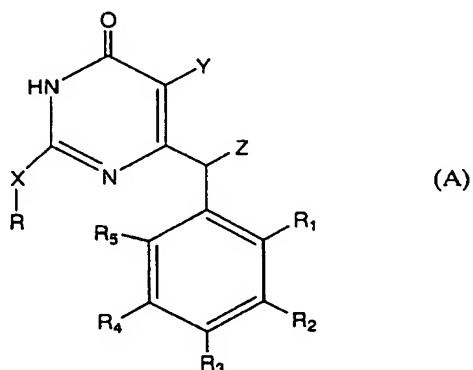
A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system.

20 Currently available drugs for AIDS therapy are divided into two groups: those that prevent infection of target cells [nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)], and those that prevent HIV-1-infected cells from yielding infectious viruses (protease inhibitors). Monotherapy with antiretroviral agents has shown limited effects, very likely due to the interplay of phenomena such as: high viral loads and
25 multiplication rates of HIV, incomplete inhibition of viral replication and emergence of drug resistant mutants. For this reason, combination therapies with two or more drugs have been proposed for a more effective treatment of AIDS. Potent suppression of HIV replication over prolonged periods has been accomplished with regimens including reverse transcriptase and protease inhibitors, although on stopping therapies viraemia has rapidly reappeared. In the
30 attempt to obtain better results, research is now focused on exploiting new targets and enhancing the activity of "old" drugs. Among the latter, NNRTs possibly endowed with better pharmacokinetic profiles, capability to inhibit clinically relevant mutants and, hopefully, to minimize HIV multiplication are being pursued.

Compounds of the present invention are dihydro-alkyloxy-benzyl-oxypyrimidines (DABOs) which potently inhibit HIV multiplication targeting reverse transcriptase without bioactivation.

5 BRIEF DESCRIPTION OF THE INVENTION

Novel compounds of formula A:



10

as herein defined, are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

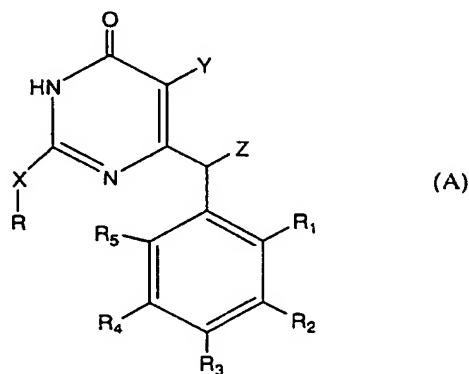
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DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

20

This invention is concerned with the compounds of formula A described below, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of

the resulting acquired immune deficiency syndrome (AIDS). The compounds of this invention include those with structural formula A:



5 wherein:

X is -O, -CH₂, -CHK (wherein K is -H, -C₁₋₄ alkyl, -C₃₋₆ Cycloalkyl), -S, -NK (wherein K is -H, -C₁₋₄ alkyl, -C₃₋₆ cycloalkyl), -aryl, -arylalkyl;

10 **R** is -H, -C₁₋₄ alkyl (containing one or more of heteroatoms like O, S, N), -C₃₋₆ cycloalkyl (containing one or more of heteroatoms like O, S, N), -aryl, -arylalkyl, heterocycle;

Y is -H, -C₁₋₄ alkyl, -C₃₋₆ cycloalkyl;

15 **Z** is -H, -C₁₋₄ alkyl, -C₃₋₆ cycloalkyl;

R₁ is -H, -C₁₋₄ alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl);

20 **R₂** is -H, -C₁₋₄ alkyl, -halogen, -NO₂, (wherein W is -H, -CH₃, -aryl); -SW (wherein W is -H, -CH₃, -aryl);

R₃ is -H, -C₁₋₄ alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl); -SW (wherein W is -H, -CH₃, -aryl)

25 **R₄** is -H, -C₁₋₄ alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl); -SW (wherein W is -H, -CH₃, -aryl)

30 **R₅** is -H, -C₁₋₄ alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl);

- pharmaceutically acceptable salts or soluble derivatives thereof;
- preparation process of derivatives thereof;

- a method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of compounds claimed;
- a pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising
5 an effective amount of compounds claimed, and a pharmaceutically acceptable carrier;
- a pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS, comprising an effective amount of compounds claimed, and a pharmaceutically acceptable carrier.

The most preferred compounds of this invention are those of table 1.

10 The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable occurs more than one time in any constituent or in formula A of this invention, its definition on each occurrence is independent of its definition at every other
15 occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "Halogen" or "Hal" as used herein, means fluoro, chloro, bromo and iodo.

20 As used herein, with exceptions as noted, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, biphenyl.

The term heterocycle or heterocyclic, as used herein except where noted represents a
25 stable 5- to 7-membered monocyclic or stable 8- to 11 -membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S; and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-
30 defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

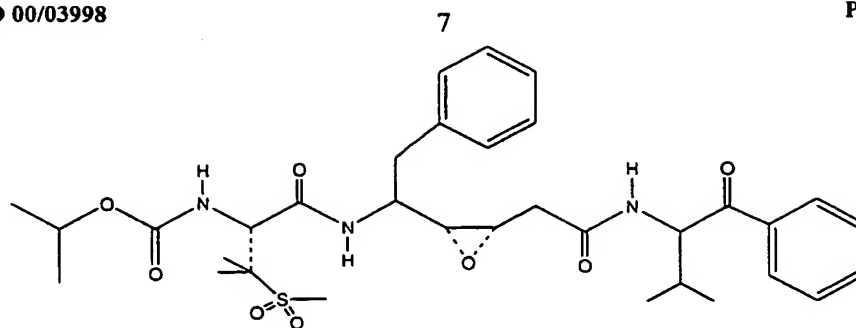
The pharmaceutically-acceptable salts of the novel compounds of this invention that are capable of salt formation (in the form of water- or oil- soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g.; from inorganic or organic acids or bases.

5 In preferred embodiments, a compound of the present invention is administered in combination or alternation with AZT, D4T, FTC (2'.3'-dideoxy-3'-thia-5-fluorocytidine); 3TC (Epivir, Glaxo Wellcome, Inc.), AZDU (3'-Azido-2',3'-dideoxyuridine); 141W94 (amprenavir, GlaxoWellcome, Inc.); Viramune (nevirapine), Rescriptor (delavirdine); or DMP-266 (efavirenz). Other examples of antiviral agents that can be used in combination or
10 alternation with the compounds disclosed herein for HIV therapy include DDI, DDC, Delaviridine, β -LddA, β -L-3'-azido-d5FC, carbovir, acyclovir, interferon, stavudine, CS-92 (3'-azido-2',3'-dideoxy-5-methyl-cytidine), 3'-azido nucleosides, and β -D-dioxolane nucleosides such as β -D-dioxolanylguanine (DXG), β -D-dioxolanyl-2,6-diaminopurine (DAPD), and β -D-dioxolanyl-6-chloropurine (ACP).

15 Preferred protease inhibitors include indinavir ({1(1,S,2R),5(S)}-2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentoamide sulfate; Merck), nelfinavir (Agouron), ritonavir (Abbot), and saquinavir (Invirase; Roche).

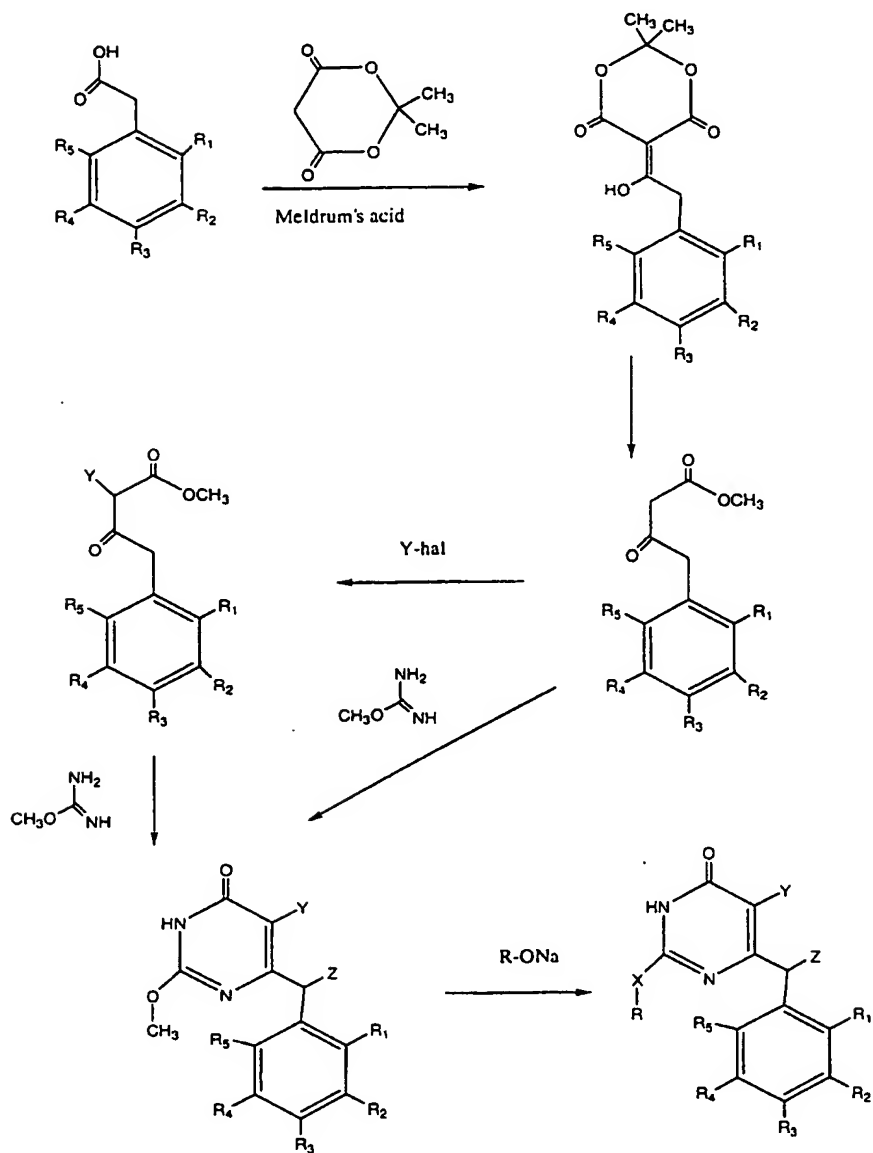
Nonlimiting examples of other compounds that can be administered in combination or
20 alternation with the compounds of the present invention to augment the properties of the drug on administration include abacavir: (1S,4R)-4-[2-amino-6-cyclopropyl-amino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate (1592U89, a carbovir analog; Glaxo Wellcome); zidovudine: AZT, 3'-azido-3'-deoxythymidine (Glaxo Wellcome); BILA 1906: N-{1S-[[[3-[2S-[(1,1-dimethylethyl)amino]carbonyl]-4R-]3-pyridinylmethyl)thio]-1-piperidinyl]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl}-2-
25 quinolinecarboxamide (Bio Mega/Boehringer-Ingelheim); BILA 2185: N-(1,1-dimethylethyl)-1-[2S-[[[2-2,6-dimethylphenoxy)-1-oxoethyl]amino]-2R-hydroxy-4-phenylbutyl]4R-pyridinylthio)-2-piperidinecarboxamide (Bio Mega/Boehringer-Ingelheim); BM+51.0836: triazoloisoindolinone derivative; BMS 186,318: aminodiol derivative HIV-1
30 protease inhibitor (Bristol-Myers-Squibb); d4API: 9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine (Gilead); stavudine: d4T, 2',3'-didehydro-3'-deoxythymidine (Bristol-Myers-Squibb); efavirenz: DMP-266, a 1,4-dihydro-2H-3, 1-benzoxazin-2-one; HBY097: S-4-

isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1H)-thione;
HEPT: 1-[(2-hydroxyethoxy)methyl]6-(phenylthio)thymine; KNI-272: (2S,3S)-3-amino-2-
hydroxy-4-phenylbutyric acid-containing tripeptide; L-697,593; 5-ethyl-6-methyl-3-(2-
phthalimido-ethyl)pyridin-2(1H)-one; L-735,524: hydroxy-aminopentane amide HIV-1
5 protease inhibitor (Merck); L-697,661: 3-{[(4,7-dichloro-1,3-benzoxazol-2-
yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one; L-FDDC: (-)-β-L-5-fluoro-2',3'-
dideoxycytidine; L-FDOC: (-)-β-L-5-fluoro-dioxolane cytosine; 6-benzyl-1-ethoxymethyl-5-
isopropyluracil (I-EBU; Triangle/Mitsubishi); nevirapine: 11-cyclopropyl-5,11-dihydro-4-
methyl-6H-dipyridol[3,2-b:2',3'-e]diazepin-6-one (Boehringer-Ingelheim); PFA:
10 phosphonoformate (foscarnet; Astra); PMEA: 9-(2-phosphonylmethoxyethyl) adenine
(Gilead); PMPA: (R)-9-(2-phosphonyl-methoxypropyl)adenine (Gilead); Ro 31-8959:
hydroxythethylamine derivative HIV-1 protease inhibitor (Roche); RPI-3121: peptidyl
protease inhibitor, 1-[(3S)-3-(n-alpha-benzyloxycarbonyl)-1-asparginyl]-amino-2-hydroxy-4-
phenylbutyryl]-n-tert-butyl-1-proline amide; 2720: 6-chloro-3,3-dimethyl-4-
15 (isopropenyloxycarbonyl)-3,4-dihydro-quinoxalin-2(1H)thione; SC-52151: hydroxyethylurea
isostere protease inhibitor (Searle); SC-55389A: hydroxyethyl-urea isostere protease inhibitor
(Searle); TIBO R82150: (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-
butenyl)imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione (Janssen); TIBO 82913: (+)-(5S)-
4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1jk]-
20 [1,4]benzodiazepin-2(1H)-thione (Janssen); TSAO-m3T:[2',5'-bis-O-(tert-
butyldimethylsilyl)-3'-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide)]- β-D-
pentofuranosyl-N3-methylthymine; U90152: 1-[3-[(1-methylethyl)-amino]2-pyridinyl]-4-[[5-
[(methylsulphonyl)-amino]-1H-indol-2yl]carbonyl]piperazine; UC: thiocarboxanilide
derivatives (Uniroyal); UC-781 =N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-
25 furancarbothioamide; UC-82 = N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-
thiophenecarbothioamide; VB 11,328: hydroxyethylsulphonamide protease inhibitor
(Vertex); VX-478: amprenavir, 141W94, hydroxyethylsulphonamide protease inhibitor
(Vertex/Glaxo Wellcome); XM 323: cyclic urea protease inhibitor (Dupont Merck),
delaviridine (Pharmacia Upjohn), famciclovir, ganciclovir, and penciclovir. In another
30 embodiment, a compound of the present invention is administered in combination with
LG1350, which has the following structure.



Preparation Of Methyl Arylacetylalkylacetates

SCHEME A



Anhydrous pyridine (400 mmoles, 32.5 ml) was added with stirring under nitrogen atmosphere into an ice-cooled solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (165 mmoles, 23.75 g) in anhydrous dichloromethane (50 ml). The resulting solution was treated, over a 2 h period at 0°C under nitrogen atmosphere, with a solution of crude
5 arylacetyl chloride in anhydrous dichloromethane (50 ml). Arylacetyl chloride was prepared before use by refluxing the proper arylacetic acid (43.2 mmoles) with thionyl chloride (21.3 ml) under nitrogen atmosphere for 2 h. Then, the mixture was stirred for 2 h at room temperature, poured into crushed ice and treated with 2N HCl (100 ml). The organic layer was separated and the aqueous solution was extracted twice with dichloromethane (25 ml).
10 The organic phase and the extracts were combined, washed with brine, dried and evaporated. The solid residue was dissolved in anhydrous methanol (250 ml) and the solution was refluxed for 20 h. After cooling, metal sodium (0.16 g-atoms, 3.68 g) was carefully added and the mixture was stirred until dissolution was complete. Alkyl halide (160 mmoles) was dropped into the solution and the resulting mixture was heated at reflux for 4-12 h. After
15 cooling, the solvent was removed and the residue treated with water (200 ml) and extracted with chloroform (3 x 100 ml). The organic layer was washed with brine (2 x 100 ml), dried and evaporated to give the desired compound, which was purified by passing through a silica gel column (chloroform as eluent).

In the above reaction, arylacetic acid (Scheme "A") or arylacetyl chloride can be
20 replaced with the corresponding 1-arylacetylimidazolid (Scheme "B") or with arylacetyloxy carbonyl anhydride, whereas the Meldrum's acid can be replaced with ethyl acetylacetate, ethyl alkylmalonate or ethyl alkylmalonate potassium salt, to give the proper ethyl arylacetylalkylacetates in high yields.

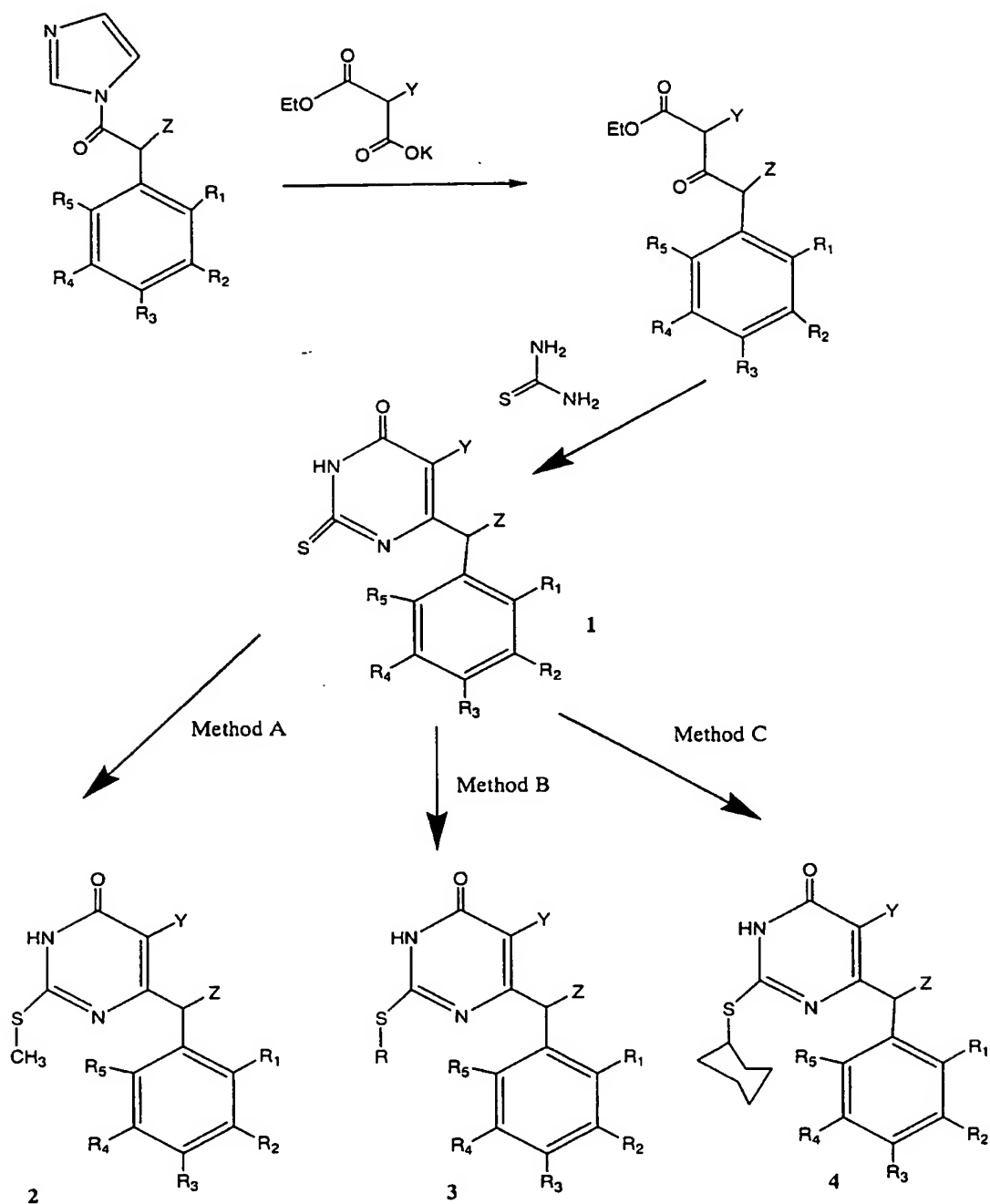
25 Preparation Of Compounds (I) With X = O (Scheme A).

The proper methyl arylacetylalkylacetate (10 mmoles) in methanol (50 ml) was added to a well-stirred suspension of O-methylisourea hydrogen sulphate (15 mmoles, 2.58 g) and calcium hydroxide (16 mmoles, 1.18 g) in water (50 ml). The resulting mixture was stirred at
30 room temperature for 72 h, then concentrated, made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried and evaporated to dryness. The residue was purified by crystallization

from the proper solvent yielding pure 5-alkyl-6-benzyl-3,4-dihydro-2-methoxypyrimidin-4-one. This compound was then refluxed with the proper potassium alkoxide (100 mmoles of potassium metal in 20-30 ml of alcohol freshly distilled on sodium metal) under nitrogen atmosphere until starting material disappeared at the TLC control. After cooling, the mixture
5 was concentrated, made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed once with brine (100 ml), dried and evaporated to give the required 2-alkoxy-5-alkyl-6-benzyl-3,4-dihydropyrimidin-4-one derivative, which was recrystallized from a suitable solvent or purified by column chromatography (silica gel; ethyl acetate:chloroform 1:1). Physical and chemical data of
10 representative compounds of the invention are reported in table 1; cytotoxicity and anti-HIV-1 activity data are reported in table 2.

Preparation Of Compounds (I) With X = S

SCHEME B



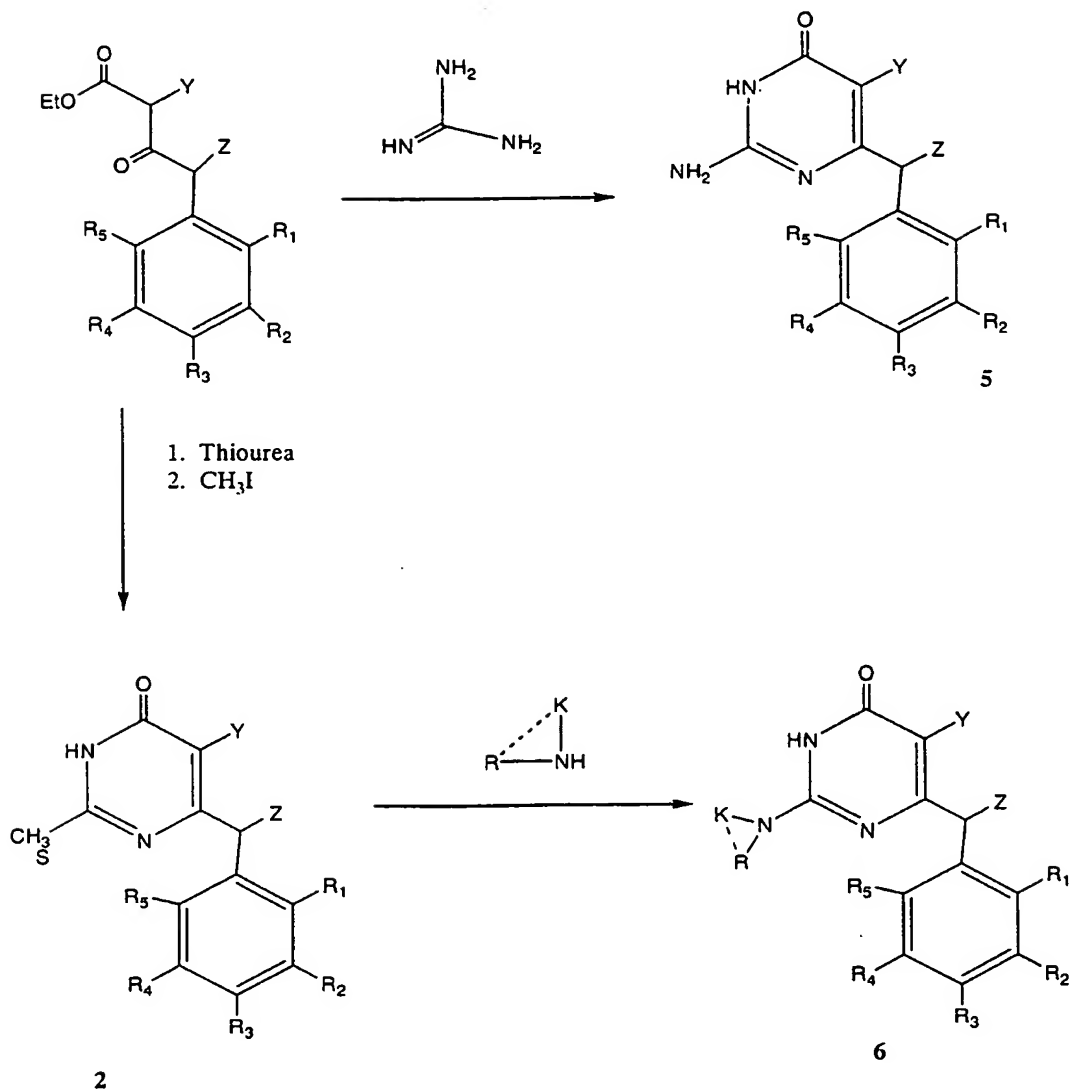
The proper ethyl arylacetylalkylacetate (31.5 mmoles) was successively added to a stirred solution of sodium metal (0.063 g-atoms) in 50 mL of absolute ethanol (50 ml) thiourea (43 mmoles). The mixture was heated while stirring at reflux for 5 h. After cooling, the solvent was distilled *in vacuo* at 40-50°C until dryness and the residue was dissolved in water (200 mL) and made acid (pH 5) with 0.5N acetic acid. The resulting precipitate (the crude 2-thiouracil derivative) was filtered under reduced pressure, washed with diethyl ether, vacuum dried at 80°C for 12 h and then crystallized from the proper solvent.

Then, according to method A, iodomethane (8 mmoles, 1.13 g) was added to a suspension containing the proper 2-thiouracil derivative (4 mmoles) in anhydrous N,N-dimethylformamide (2 ml), and the resulting mixture was stirred at room temperature until the starting material disappeared at the TLC control (silica gel; n-hexane: ethyl acetate: methanol 12:3:1). Then the reaction content was poured on cold water (100 mL) and extracted with ethyl acetate (3 x 50 ml). The organic layers were collected, washed with a sodium thiosulfate solution (100 ml), brine (3 x 50 ml), dried and evaporated to furnish the crude 5-alkyl-6-benzyl-3,4-dihydro-2-methylthiopyrimidin-4-one (2) as a solid purified by crystallization.

Alternatively, according to methods B and C, potassium carbonate (4.2 mmoles) and the proper alkyl halide (4.4 mmoles) were added to a suspension containing 2-thiouracil derivative (4 mmoles) in anhydrous N,N-dimethylformamide (2 ml). The resulting mixture was stirred at room temperature (method B) or at 80°C (method C) until starting material disappeared at the TLC control (silica gel; n-hexane:ethyl acetate:methanol 12:3:1). Then the reaction content was poured on cold water (200 mL), made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The organic layers were collected, washed with a sodium thiosulfate solution (100 ml), brine (100 ml), dried and evaporated to furnish 5-alkyl-6-benzyl-3,4-dihydro-2-methylthiopyrimidin-4-ones (3) and (4) as crude material which was then purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate:methanol 12:3:1) followed by crystallization. Physical and chemical data of representative compounds of the invention are reported in table 1. Cytotoxicity and anti-HIV-1 activity in vitro are reported in table 2.

Preparation Of Compounds (I) With X = NK

SCHEME C



Title derivatives were prepared according to the procedure described for the synthesis of compounds with $X = S$ (I), using ethyl arylacetylalkylacetates and guanidine [2-amino-6-benzylpyrimidin-4-ones (5)] as starting materials. 2-Alkylaminoderivatives (6) were synthesized by heating the previously reported 5-alkyl-6-benzyl-3,4-dihydro-2-methylthio pyrimidin-4-ones with 20-30 ml of proper amine in a sealed tube at 170°C for 24 h. Physical and chemical data of some compounds (6) are reported in table 1. Cytotoxicity and anti-HIV-1 activity in vitro are reported in table 2. The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are also useful in the preparation and execution of screening for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antiviral to HIV reverse transcriptase e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes. For inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS or ARC, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of the present invention. These

pharmaceutical compositions may be in the form of orally administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient; such as cocoa butter, synthetic glyceride, esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidity and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 75 mg/kg body weight. One preferred dosage range is 1 to 50 mg/kg body weight orally. Another preferred dosage range is 5 to 75 mg/kg body weight orally. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of

excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. The compounds of this invention can be administered in combination with other compounds that are HIV reverse transcriptase inhibitors, and/or with compounds that are HIV protease inhibitors. When used in a combination treatment with compounds of the instant invention, dosage levels of HIV protease inhibitors of the order of 1 to 25 or 50 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two- to-five time higher. For example, infection by HIV is effectively treated by the administration of from 5 to 25 milligrams of the HIV protease inhibitor per kilogram of body weight from one to three times per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Dosages of HIV reverse transcriptase inhibitors, when used in a combination treatment with compounds of the present invention, are comparable to those dosages specified above for the present compounds. It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals includes any combination with any pharmaceutical composition useful for the treatment of AIDS.

ANTIVIRAL ASSAY PROCEDURES

Compounds. Compounds were solubilized in DMSO at 200 mM and then diluted into culture medium.

Cells and viruses. MT-4, C8166, H9/IIIB and CEM cells were grown at 37 °C in a 5% CO₂ atmosphere in RPMI 1640 medium, supplemented with 10% fetal calf serum (FCS), 100 IU/mL penicillin and 100 µg/mL streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco). Human

immunodeficiency virus type-1 (HIV-1, III_B strain) was obtained from supernatants of persistently infected H9/III_B cells. HIV-1 stock solution had a titres of 4.5×10^6 50% cell culture infectious dose (CCID₅₀)/ml.

HIV titration. Titration of HIV was performed in C8166 cells by the standard limiting dilution method (dilution 1:2, four replica wells per dilution) in 96-well plates. The infectious virus titre was determined by light microscope scoring of cytopathicity after 4 days of incubation and the virus titres were expressed as CCID₅₀/mL.

Anti-HIV assays. Activity of the compounds against HIV-1 and HIV-2 multiplication in acutely infected cells was based on the inhibition of virus-induced cytopathicity in MT-4 and C8166 cells, respectively. Briefly, 50 µL of culture medium containing 1×10^4 cells were added to each well of flat-bottom microtiter trays containing 50 µl of culture medium with or without various concentrations of the test compounds. Then 20 µL of an HIV suspension containing 100 CCID₅₀ were added. After a 4-day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity. It was based on the viability of mock-infected cells, as monitored by the MTT method.

RT assays. Assays were performed as follows. Briefly, purified rRT was assayed for its RNA-dependent polymerase-associated activity in a 50 µL volume containing: 50 mM TrisHCl (pH 7.8), 80 mM KCl, 6mM MgCl₂, 1 mM DTT, 0.1 mg/ mL BSA, 0.3 OD₂₆₀ unit/mL template:primer [poly(rC)-oligo(dG)12-18] and 10 µM [³H]dGTP (1 Ci/mmol). After incubation for 30 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

EXAMPLES

2-Cyclopentylthio-6-(2,6-difluorophenylmethyl)-3,4-dihydroxyrimidin-4-(3H)-one (MC867).

A mixture of 6-(2,6-difluorophenylmethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (0.16 g, 0.65 mmol; prepared as reported in scheme B), cyclopentyl bromide (0.11 g, 0.08 mL, 0.71 mmol) and potassium carbonate (0.09 g, 0.65 mmol) in 1 mL of anhydrous DMF was stirred at room temperature for 24 h. After treatment with cold water (200 mL), the solution was extracted with ethyl acetate (3 x 50 mL). The organic layers were collected, washed with brine (3 x 50 mL), dried and evaporated to furnish crude MC867, which was

purified by chromatography on silica gel column (eluent: n-hexane/ethyl acetate/methanol 12/3/1).

Yield (%): 45; mp (°C): 168-169; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{16}H_{16}F_2N_2OS$ (322.37).

5

2-Cyclopentylthio-6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methylpyrimidin-4-(3H)-one (MC922).

The synthesis of MC922 was accomplished according to the above reported procedure starting from 6-(2,6-difluorophenylmethyl)-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin-4-(3H)-one (see scheme B).

10

Yield (%): 54; mp (°C): 192-193; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{17}H_{18}F_2N_2OS$ (336.40).

2-Cyclopentylthio-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydropyrimidin-4-(3H)-one (MC1008)

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The synthesis of MC1008 was accomplished according to the above reported procedure starting from 6-[1-(2,6-difluorophenyl)ethyl]-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (see scheme B).

Yield (%): 54; mp (°C): 165.5-166.5; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{17}H_{18}F_2N_2OS$ (336.40).

20

2-Cyclopentylthio-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methylpyrimidin-4(3H)-one (MC1047)

The synthesis of MC1047 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (see scheme B).

25

Yield (%): 60; mp (°C): 196-197; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{18}H_{20}F_2N_2OS$ (350.43).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-(methylthiomethyl)thiopyrimidin-4-(3H)-one (MC1161)

The synthesis of MC1161 was accomplished according to the above reported procedures, starting from 6-(2,6-difluorophenylmethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 72; mp (°C): 159-160; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{13}H_{12}F_2N_2OS_2$ (314.37).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-5-methyl-2-(methylthiomethyl)thiopyrimidin-4(3H)-one (MC1162).

The synthesis of MC1162 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 70; mp (°C): 183-184; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{14}H_{14}F_2N_2OS_2$ (328.39).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-5-(1-methylethyl)-2-(methylthiomethyl)thiopyrimidin-4-(3H)-one MC1145).

The synthesis of MC1145 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-5-(1-methylethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 62; mp (°C): 158.5-160; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{16}H_{18}F_2N_2OS_2$ (356.45).

2-Cyclopentylamino-6-(2,6-difluorophenylmethyl)-3,4-dihydropyrimidin-4-(3H)-one (MC1022).

Cyclopentylamine (10 mL) was heated while stirring with 6-(2,6-difluorophenylmethyl)-3,4-dihydro-2-methylthiopyrimidin-4-(3H)-one (0.30 g, 1.12 mmol; prepared as reported in scheme B or C) in a sealed tube at 160°C for 10 h. After cooling, the mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were collected, washed with brine (3 x 50 mL), dried and evaporated to furnish crude MC1022,

which was purified by chromatography on silica gel column (eluent: ethyl acetate/chloroform 1/1).

Yield (%): 74; mp (°C): - (oil); formula (molecular weight): $C_{16}H_{17}F_2N_3O$ (305.33).

- 5 2-Cyclopentylamino-6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methylpyrimidin-4-(3H)-one (MC1050).

The synthesis of MC1050 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methyl-2-methylthiopyrimidin-4(3H)-one (see scheme B or C).

- 10 Yield (%): 60; mp (°C): 115-117; recrystallization solvent: n-hexane/cyclohexane; formula (molecular weight): $C_{17}H_{19}F_2N_3O$ (319.35).

2-Cyclopentylamino-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydropyrimidin-4-(3H)-one (MC1048).

- 15 The synthesis of MC1048 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-2-methylthiopyrimidin-4(3H)-one (see scheme B or C).

Yield (%): 48; mp (°C): - (oil); formula (molecular weight) $C_{17}H_{19}F_2N_3O$ (319.35).

- 20 2-Cyclopentylamino-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methylpyrimidin-4-(3H)-one (MC1129)

The synthesis of MC1129 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methyl-2-methylthiopyrimidin-4(3H)-one (see scheme B or C).

- 25 Yield (%): 38; mp (°C): - (oil); formula (molecular weight): $C_{18}H_{21}F_2N_3O$ (333.38).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-(4-thiomorpholin-1-yl)pyrimidin-4-(3H)-one (MC1193).

- 30 The synthesis of MC1193 was accomplished according to the above reported procedure, starting from thiomorpholine and 6-(2,6-difluorophenylmethyl)-3,4-dihydro-2-methylthiopyrimidin-4(3H)-one (see scheme B or C).

Yield (%): 78; mp (°C): 233-234; recrystallization solvent: acetonitrile; formula (molecular weight): $C_{15}H_{15}F_2N_3OS$ (323.36).

5 6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-*N,N*-dimethylaminopyrimidin-4-(3*H*)-one
(MC1182).

To a stirred solution of sodium metal (0.14 g, 6.3 mg-atoms) in absolute ethanol (50 mL) 1,1-dimethylguanidine sulfate (1.17 g, 4.3 mmol) and ethyl 4-(2,6-difluorophenyl)acetylacetate (0.76 g, 3.15 mmol) were successively added. The mixture was heated while stirring at reflux for 8 h. After cooling, the solvent was distilled *in vacuo* at 40-50°C until dryness and the
10 residue was dissolved in water (200 mL) and made acid (pH 5) with 0.5N acetic acid. The resulting precipitate (the crude isocytosine derivative) was filtered under reduced pressure, washed with diethyl ether, vacuum dried at 80°C for 12 h and then crystallized from benzene/cyclohexane (see scheme C starting from ethyl 4-(2,6-difluorophenyl)acetylacetate and replacing guanidine hydrochloride with 1,1-dimethylguanidine sulfate).
15 Yield (%): 88; mp (°C): 210-211; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{13}H_{13}F_2N_3O$ (265.26).

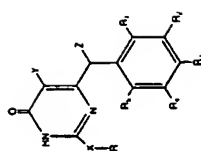


Table 1. Physical and Chemical Data of MC Compounds

| Compl. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | m.p., °C | Recryst. Solvent | % yield | Formula * |
|---------|---|----|----|----------------------------|-----------------|-----------------|------------------|----------------|----------------|-------------|-----------------------------|---------|--------------------------------------------------------------------------------|
| MC 507 | O | H | H | 2,5-Me ₂ -c-hex | H | H | H | H | H | 130-132 | Petrol. Ether/diethyl ether | 22 | C ₁₉ H ₂₄ N ₂ O ₂ |
| MC 508 | O | H | H | 4,5-Me ₂ -c-hex | H | H | H | H | H | 132-134 | Petrol. Ether/diethyl ether | 28 | C ₁₉ H ₂₄ N ₂ O ₂ |
| MC 512 | O | H | H | 3,5-Me ₂ -c-hex | H | H | H | H | H | 178-181 | Petrol. Ether/diethyl ether | 12 | C ₁₉ H ₂₄ N ₂ O ₂ |
| MC 531 | O | Me | H | 2,5-Me ₂ -c-hex | H | H | H | H | H | 196-198 | Petrol. Ether/diethyl ether | 18 | C ₂₀ H ₂₆ N ₂ O ₂ |
| MC 1114 | O | H | H | Sec-but | F | H | H | H | F | 87-88 | Petrol. Ether/diethyl ether | 28 | C ₁₈ H ₂₂ F ₂ N ₂ O ₂ |
| MC 1103 | O | H | H | c-pent | F | H | H | H | F | 183.5-184.5 | Hexane | 52 | C ₁₈ H ₂₂ F ₂ N ₂ O ₂ |
| MC 843 | S | H | H | benzylloxymeth | H | H | H | H | H | 181-183 | Cyclohexane/benzene | 38 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 796 | S | H | Ph | Sec-but | H | H | H | H | H | 157-158 | n-hexane/cyclohexane | 78 | C ₂₁ H ₂₈ N ₂ O ₂ S |
| MC 890 | S | H | Me | Iso-prop | H | H | H | H | H | 118-119 | n-hexane | 88 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 892 | S | H | Me | c-pent | H | H | H | H | H | 95-96 | n-hexane | 65 | C ₁₇ H ₂₀ N ₂ O ₂ S |
| MC 898 | S | H | Me | c-hex | H | H | H | H | H | 142-143 | n-hexane | 59 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 899 | S | H | Et | Iso-prop | H | H | H | H | H | 144-145 | Cyclohexane | 85 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 900 | S | H | Et | c-pent | H | H | H | H | H | 168-169 | Cyclohexane | 69 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 903 | S | H | Et | c-hex | H | H | H | H | H | 175.5-176.5 | Cyclohexane | 60 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 806 | S | H | H | Sec-but | Me | H | H | H | H | 118-119 | n-hexane/cyclohexane | 67 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 842 | S | H | H | c-pent | Me | H | H | H | H | 142-144 | Cyclohexane | 61 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 809 | S | H | H | Sec-but | H | H | Me | H | H | 107.5-108.5 | n-hexane | 56 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 817 | S | H | H | Sec-but | NO ₂ | H | H | H | H | 127-128 | Cyclohexane/benzene | 68 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 897 | S | H | H | Sec-but | H | NO ₂ | H | H | H | 128-130 | Cyclohexane/benzene | 54 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 863 | S | H | H | Sec-but | H | H | NO ₂ | H | H | 120-121 | Petrol. Ether/diethyl ether | 100 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 854 | S | H | H | Sec-but | Cl | H | H | H | H | 98-99 | Cyclohexane | 92 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 857 | S | H | H | Sec-but | H | Cl | H | H | H | 125-126 | Cyclohexane | 74 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 859 | S | H | H | Sec-but | F | H | H | H | H | 106-107 | n-hexane/cyclohexane | 68 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 880 | S | H | H | Sec-but | H | F | H | H | H | 96-97 | Cyclohexane | 67 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 884 | S | H | H | Sec-but | H | F | H | H | H | 98-99 | n-hexane | 94 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 825 | S | H | H | Sec-but | NH ₂ | H | H | H | H | 143-144 | Cyclohexane/benzene | 74 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 900 | S | H | H | Sec-but | H | H | NH ₂ | H | H | 128-130 | Cyclohexane | 77 | C ₁₉ H ₂₄ N ₂ O ₂ S |
| MC 868 | S | H | H | Sec-but | CF ₃ | H | H | H | H | 125-126 | Cyclohexane | 89 | C ₁₉ H ₂₄ F ₃ N ₂ O ₂ S |
| MC 959 | S | H | H | Sec-but | H | H | ClF ₃ | H | H | 144-145 | Cyclohexane | 75 | C ₁₉ H ₂₄ F ₃ N ₂ O ₂ S |
| MC 952 | S | H | H | Sec-but | OMe | H | H | H | H | 123-124 | Cyclohexane | 69 | C ₁₉ H ₂₄ N ₂ O ₂ S |

Table 1. Physical and Chemical Data of MC Compounds (continued)

| Compd. | X | Y | Z | R | R' | R ² | R ³ | R ⁴ | m.p., °C | Recryst. Solvent | % yield | Formula |
|---------|---|----|----|----------|-------------|-----------------|-----------------|----------------|-------------|----------------------|---------|-------------------------------------------------------------------------------|
| MC 957 | S | H | H | Sec-but | H | OMe | H | H | 78-80 | n-hexane/Cyclohexane | 71 | C ₁₆ H ₃₀ N ₂ O ₅ |
| MC 964 | S | H | H | Sec-but | H | OMe | H | H | 112-113 | Cyclohexane | 63 | C ₁₆ H ₃₀ N ₂ O ₅ |
| MC 1041 | S | H | H | Sec-but | H | F | H | H | 122-123 | Cyclohexane | 68 | C ₁₆ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1042 | S | H | H | Sec-but | H | Me | H | H | 119-120 | n-hexane | 72 | C ₁₇ H ₃₂ N ₂ O ₅ |
| MC 877 | S | H | H | Me | Cl | H | H | Cl | 237-238 | benzene | 98 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 878 | S | H | H | iso-prop | Cl | H | H | Cl | 230-231 | benzene | 81 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 886 | S | H | H | n-but | Cl | H | H | Cl | 153-154 | cyclohexane | 62 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 885 | S | H | H | iso-but | Cl | H | H | Cl | 143.5-144.5 | cyclohexane | 56 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 815 | S | H | H | sec-but | Cl | H | H | Cl | 183-184 | cyclohexane/benzene | 55 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 888 | S | H | H | c-pent | Cl | H | H | Cl | 185-186 | cyclohexane | 54 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 891 | S | H | H | c-hex | Cl | H | H | Cl | 200-201 | cyclohexane/benzene | 49 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 871 | S | H | H | Me | F | H | H | F | 197-198 | benzene | 95 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 860 | S | H | H | iso-prop | F | H | H | F | 174-175 | cyclohexane | 74 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 872 | S | H | H | n-but | F | H | H | F | 126-127 | cyclohexane | 46 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 866 | S | H | H | iso-but | F | H | H | F | 136-137 | cyclohexane | 49 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 848 | S | H | H | sec-but | F | H | H | F | 149-150 | n-hexane/cyclohexane | 48 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 867 | S | H | H | c-pent | F | H | H | F | 168-169 | cyclohexane | 45 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 870 | S | H | H | c-hex | F | H | H | F | 164-165 | cyclohexane | 40 | C ₁₇ H ₂₆ F ₂ N ₂ O ₅ |
| MC 1001 | S | H | Me | iso-prop | Cl | H | H | Cl | 196-196.5 | cyclohexane/benzene | 52 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 996 | S | H | Me | c-pent | Cl | H | H | Cl | 181-182 | cyclohexane | 45 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 1016 | S | H | Me | c-hex | Cl | H | H | Cl | 211-212 | cyclohexane/benzene | 42 | C ₁₇ H ₂₆ Cl ₂ N ₂ O ₅ |
| MC 1000 | S | H | Et | iso-prop | Cl | H | H | Cl | 166-168 | diethyl ether | 54 | C ₁₈ H ₃₀ Cl ₂ N ₂ O ₅ |
| MC 1002 | S | H | Et | c-pent | Cl | H | H | Cl | 168-169 | diethyl ether | 40 | C ₁₈ H ₃₀ Cl ₂ N ₂ O ₅ |
| MC 1003 | S | H | Et | c-hex | Cl | H | H | Cl | 198-199 | cyclohexane | 41 | C ₁₈ H ₃₀ Cl ₂ N ₂ O ₅ |
| MC 1007 | S | H | Me | iso-prop | F | H | H | F | 155-156 | cyclohexane | 53 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1044 | S | H | Me | iso-but | F | H | H | F | 159-160 | cyclohexane | 49 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1045 | S | H | Me | n-but | F | H | H | F | 149-150 | cyclohexane | 58 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1110 | S | H | Me | sec-but | F | H | H | F | 133-134 | n-hexane | 75 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1008 | S | H | Me | c-pent | F | H | H | F | 165.5-166.5 | cyclohexane | 60 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1013 | S | H | Me | c-hex | F | H | H | F | 206-207 | benzene | 44 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1005 | S | H | Et | iso-prop | F | H | H | F | 149-150 | cyclohexane | 40 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1006 | S | H | Et | c-pent | F | H | H | F | 141-143 | cyclohexane | 45 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 1014 | S | H | Et | c-hex | F | H | H | F | 154-155 | cyclohexane | 51 | C ₁₈ H ₂₈ F ₂ N ₂ O ₅ |
| MC 971 | S | H | Me | iso-prop | Cl=CH-CH=CH | Cl | H | H | 161-162 | n-hexane/cyclohexane | 58 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 972 | S | H | Me | c-pent | Cl=CH-CH=CH | Cl | H | H | 140-141 | n-hexane/cyclohexane | 49 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 974 | S | H | Me | c-hex | Cl=CH-CH=CH | Cl | H | H | 177-178 | n-hexane | 45 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 969 | S | H | Et | iso-prop | Cl=CH-CH=CH | Cl | H | H | 163-164 | cyclohexane | 54 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 973 | S | H | Et | c-pent | Cl=CH-CH=CH | Cl | H | H | oil | -- | 48 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 975 | S | H | Et | c-hex | Cl=CH-CH=CH | Cl | H | H | 126-127 | n-hexane | 41 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 844 | S | Me | H | sec-but | Me | H | H | H | 177-178 | cyclohexane | 55 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 845 | S | Me | H | sec-but | H | H | Me | H | 123-128 | n-hexane | 61 | C ₁₉ H ₃₀ N ₂ O ₅ |
| MC 925 | S | Me | H | sec-but | H | NO ₂ | H | H | 163-164 | cyclohexane/benzene | 88 | C ₁₉ H ₂₈ N ₂ O ₅ |
| MC 924 | S | Me | H | sec-but | H | H | NO ₂ | H | 178-180 | cyclohexane/benzene | 100 | C ₁₉ H ₂₈ N ₂ O ₅ |
| MC 949 | S | Me | H | sec-but | Cl | H | H | H | 170-171 | cyclohexane | 68 | C ₁₉ H ₂₈ ClN ₂ O ₅ |

Table I. Physical and Chemical Data of MC Compounds (continued)

| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | m.p., °C | Recryst. Solvent | % yield | Formula |
|--------|----|-------|----|----------|----------------|----------------|----------------|----------------|----------------|-------------|----------------------|---------|---------------------------------------------------------------------------------|
| MC910 | S | Me | II | sec-but | H | Cl | II | II | II | 145-146 | cyclohexane | 75 | C ₁₆ H ₁₈ ClN ₂ O ₂ S |
| MC911 | S | Me | II | sec-but | H | II | II | II | II | 163-165 | cyclohexane | 79 | C ₁₆ H ₁₈ ClN ₂ O ₂ S |
| MC913 | S | Me | II | sec-but | F | II | II | II | II | 120.5-121.5 | cyclohexane | 65 | C ₁₆ H ₁₈ FN ₂ O ₂ S |
| MC918 | S | Me | II | sec-but | H | F | F | II | II | 146-147 | cyclohexane | 72 | C ₁₆ H ₁₈ FN ₂ O ₂ S |
| MC919 | S | Me | II | sec-but | II | II | II | II | II | 154-155 | cyclohexane | 69 | C ₁₆ H ₁₈ FN ₂ O ₂ S |
| MC912 | S | Me | II | Me | Cl | II | II | II | II | 206-261 | benzene | 93 | C ₁₃ H ₁₂ Cl ₂ N ₂ O ₂ S |
| MC914 | S | Me | II | iso-prop | Cl | II | II | II | II | 241-242 | cyclohexane/benzene | 78 | C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S |
| MC920 | S | Me | II | n-but | Cl | II | II | II | II | 179-180 | cyclohexane | 52 | C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S |
| MC916 | S | Me | II | iso-but | Cl | II | II | II | II | 208-209 | cyclohexane | 63 | C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S |
| MC850 | S | Me | II | sec-but | Cl | II | II | II | II | 204-205 | cyclohexane | 53 | C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S |
| MC915 | S | Me | II | c-pent | Cl | II | II | II | II | 252-253 | cyclohexane/benzene | 49 | C ₁₇ H ₁₆ Cl ₂ N ₂ O ₂ S |
| MC917 | S | Me | II | c-hex | Cl | II | II | II | II | 237-238 | cyclohexane | 48 | C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S |
| MC869 | S | Me | II | Me | F | II | II | II | F | 218.5-219.5 | benzene | 92 | C ₁₃ H ₁₂ F ₂ N ₂ O ₂ S |
| MC881 | S | Me | II | iso-prop | F | II | II | II | F | 164-165 | cyclohexane | 76 | C ₁₃ H ₁₂ F ₂ N ₂ O ₂ S |
| MC905 | S | Me | II | n-but | F | II | II | II | F | 178-179 | cyclohexane | 65 | C ₁₆ H ₁₈ F ₂ N ₂ O ₂ S |
| MC921 | S | Me | II | iso-but | F | II | II | II | F | 161-162 | cyclohexane | 59 | C ₁₆ H ₁₈ F ₂ N ₂ O ₂ S |
| MC849 | S | Me | II | sec-but | F | II | II | II | F | 128-129 | n-hexane | 49 | C ₁₆ H ₁₈ F ₂ N ₂ O ₂ S |
| MC922 | S | Me | II | c-pent | F | II | II | II | F | 192-193 | cyclohexane | 54 | C ₁₇ H ₁₆ F ₂ N ₂ O ₂ S |
| MC923 | S | Me | II | c-hex | F | II | II | II | F | 191-192 | cyclohexane | 49 | C ₁₈ H ₁₈ F ₂ N ₂ O ₂ S |
| MC1060 | S | Me | Me | Me | F | II | II | II | F | 202-203 | cyclohexane/benzene | 49 | C ₁₄ H ₁₄ F ₂ N ₂ O ₂ S |
| MC1109 | S | Me | Me | sec-but | F | II | II | II | F | 135-136 | cyclohexane | 55 | C ₁₃ H ₁₂ F ₂ N ₂ O ₂ S |
| MC1047 | S | Me | Me | c-pent | F | II | II | II | F | 196-197 | cyclohexane | 60 | C ₁₄ H ₁₄ F ₂ N ₂ O ₂ S |
| MC798 | S | Et | II | sec-but | II | II | II | II | II | 140-141 | cyclohexane | 47 | C ₁₇ H ₁₂ N ₂ O ₂ S |
| MC1037 | S | Et | II | sec-but | F | II | II | II | F | 174-175 | benzene | 78 | C ₁₆ H ₁₆ F ₂ N ₂ O ₂ S |
| MC1038 | S | Et | II | sec-but | F | II | II | II | F | 150-151 | n-hexane/cyclohexane | 62 | C ₁₇ H ₁₆ F ₂ N ₂ O ₂ S |
| MC804 | S | Et | II | sec-but | Cl=CH | II | II | II | F | 198.5-199.5 | cyclohexane | 42 | C ₁₇ H ₁₆ F ₂ N ₂ O ₂ S |
| MC1039 | S | i-pro | II | iso-prop | F | II | II | II | F | 167-168 | n-hexane | 76 | C ₁₇ H ₁₆ F ₂ N ₂ O ₂ S |
| MC852 | S | allyl | II | sec-but | II | II | II | II | II | 127.5-128.5 | cyclohexane | 68 | C ₁₈ H ₁₂ N ₂ O ₂ S |
| MC856 | S | n-pro | II | sec-but | II | II | II | II | II | 108-109 | n-hexane | 42 | C ₁₇ H ₁₆ N ₂ O ₂ S |
| MC834 | S | n-but | II | sec-but | II | II | II | II | II | oil | -- | 32 | C ₁₇ H ₁₆ N ₂ O ₂ S |
| MC1119 | NH | H | II | ethyl | F | II | II | II | F | 138-140 | n-hexane/cyclohexane | 50 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1078 | NH | II | II | n-prop | F | II | II | II | F | 136-137 | cyclohexane | 49 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC979 | NH | II | II | iso-prop | F | II | II | II | F | 150-151 | diethyl ether | 58 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC980 | NH | II | II | c-prop | F | II | II | II | F | 183-184 | cyclohexane/benzene | 68 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1077 | NH | II | II | n-but | F | II | II | II | F | 130-131 | n-hexane | 60 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC945 | NH | II | II | sec-but | F | II | II | II | F | 140-141 | diethyl ether | 80 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1043 | NH | II | II | MeOethyl | F | II | II | II | F | 120-121 | acetonitrile | 78 | C ₁₈ H ₁₆ F ₂ N ₂ O ₂ |
| MC1022 | NH | H | II | c-pent | F | II | II | II | F | oil | -- | 74 | C ₁₆ H ₁₆ F ₂ N ₂ O |
| MC1049 | NH | II | Me | c-hex | F | II | II | II | F | 143-144 | diethyl ether | 45 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1048 | NH | II | II | c-pent | F | II | II | II | F | oil | -- | 48 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1118 | NH | Me | II | iso-prop | F | II | II | II | F | 165-166 | n-hexane | 53 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1130 | NH | Me | II | sec-but | F | II | II | II | F | oil | -- | 56 | C ₁₆ H ₁₆ F ₂ N ₂ O |
| MC1050 | NH | Me | II | c-pent | F | II | II | II | F | 115-117 | n-hexane/cyclohexane | 60 | C ₁₇ H ₁₆ F ₂ N ₂ O |
| MC1105 | NH | Me | II | benzyl | F | II | II | II | F | 182-183 | cyclohexane/benzene | 82 | C ₁₇ H ₁₆ F ₂ N ₂ O |

Table I. Physical and Chemical Data of MC Compounds (continued)

| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | m.p., °C | Recryst. Solvent | % yield | Formula * |
|--------|----|-------|----|-----------------------|----------------|----------------|----------------|----------------|----------------|-----------|----------------------|---------|------------------------------------------------------------------------------|
| MC1129 | NH | Me | Me | c-pent | F | H | H | H | F | oil | .. | 38 | C ₁₆ H ₁₉ F ₂ N ₂ O |
| MC1167 | NH | H | H | Me | F | H | H | H | F | 202-203 | acetonitrile | 39 | C ₁₃ H ₁₇ F ₂ N ₂ O |
| MC1168 | NH | Me | Me | Me | F | H | H | H | F | 210-211 | acetonitrile | 48 | C ₁₅ H ₁₉ F ₂ N ₂ O |
| MC1186 | NH | Me | Me | n-prop | F | H | H | H | F | 156-157 | acetonitrile | 62 | C ₁₈ H ₂₃ F ₂ N ₂ O |
| MC1185 | NH | Me | Me | n-but | F | H | H | H | F | 192-193 | acetonitrile | 68 | C ₁₉ H ₂₅ F ₂ N ₂ O |
| MC1178 | NH | H | Me | Me | F | H | H | H | F | 145-146 | acetonitrile | 34 | C ₁₅ H ₁₉ F ₂ N ₂ O |
| MC1190 | NH | H | Me | n-prop | F | H | H | H | F | oil | .. | 45 | C ₁₇ H ₂₃ F ₂ N ₂ O |
| MC1191 | NH | H | Me | iso-prop | F | H | H | H | F | oil | .. | 54 | C ₁₇ H ₂₃ F ₂ N ₂ O |
| MC1189 | NH | H | Me | n-but | F | H | H | H | F | oil | .. | 55 | C ₁₈ H ₂₅ F ₂ N ₂ O |
| MC1192 | NH | H | Me | sec-but | F | H | H | H | F | oil | .. | 59 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1180 | NH | H | Me | c-hex | F | H | H | H | F | oil | .. | 62 | C ₂₀ H ₂₉ F ₂ N ₂ O |
| MC1170 | NH | Me | Me | Me | F | H | H | H | F | 193-194 | cyclohexane/benzene | 34 | C ₁₇ H ₂₃ F ₂ N ₂ O |
| MC1187 | NH | Me | Me | n-but | F | H | H | H | F | oil | .. | 49 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1181 | NH | Me | Me | c-hex | F | H | H | H | F | oil | .. | 54 | C ₂₀ H ₂₉ F ₂ N ₂ O |
| MC1182 | N | H | H | Me ₂ | F | H | H | H | F | 210-211 | cyclohexane/benzene | 88 | C ₁₇ H ₂₃ F ₂ N ₂ O |
| MC1183 | N | H | H | Me-piperaz | F | H | H | H | F | 195-196 | acetonitrile | 84 | C ₁₈ H ₂₅ F ₂ N ₂ O |
| MC1188 | N | H | H | morph | F | H | H | H | F | 215-216 | acetonitrile | 75 | C ₁₈ H ₂₅ F ₂ N ₂ O ₂ |
| MC1193 | N | H | H | thiomorph | F | H | H | H | F | 233-234 | acetonitrile | 78 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1194 | N | H | H | piperid | F | H | H | H | F | 209-210 | acetonitrile | 68 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1196 | N | H | H | pyrrolid | F | H | H | H | F | 233-234 | acetonitrile | 52 | C ₁₈ H ₂₅ F ₂ N ₂ O |
| MC1202 | N | H | H | Et ₂ | F | H | H | H | F | 159-160 | acetonitrile | 43 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1204 | N | H | H | (n-prop) ₂ | F | H | H | H | F | 111-112 | n-hexane | 32 | C ₁₇ H ₂₃ F ₂ N ₂ O |
| MC1195 | N | Me | H | Me ₂ | F | H | H | H | F | 237-238 | acetonitrile | 80 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1203 | N | Me | H | Me-piperaz | F | H | H | H | F | 235-236 | acetonitrile | 62 | C ₁₉ H ₂₇ F ₂ N ₂ O |
| MC1205 | N | Me | H | morph | F | H | H | H | F | 244-245 | acetonitrile | 65 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1206 | N | Me | H | thiomorph | F | H | H | H | F | 255-256 | acetonitrile | 54 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1137 | S | Me | Me | iso-prop | F | H | H | H | F | 177-178 | acetonitrile | 45 | C ₁₈ H ₂₅ F ₂ N ₂ O ₂ |
| MC1175 | S | Me | Me | n-but | F | H | H | H | F | 122-123 | n-hexane | 51 | C ₁₇ H ₂₃ F ₂ N ₂ O ₂ |
| MC1153 | S | Me | Me | iso-but | F | H | H | H | F | 152-153 | cyclohexane | 58 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1174 | S | Me | Me | c-hex | F | H | H | H | F | 208-209 | cyclohexane | 48 | C ₂₀ H ₂₉ F ₂ N ₂ O ₂ |
| MC1161 | S | H | H | MeSMe | F | H | H | H | F | 159-160 | n-hexane/cyclohexane | 72 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1162 | S | Me | H | MeSMe | F | H | H | H | F | 183-184 | cyclohexane/benzene | 70 | C ₁₉ H ₂₇ F ₂ N ₂ O ₂ |
| MC1157 | S | Et | H | MeSMe | F | H | H | H | F | 153-154 | cyclohexane | 69 | C ₂₀ H ₂₉ F ₂ N ₂ O ₂ |
| MC1145 | S | i-pro | H | MeSMe | F | H | H | H | F | 158.5-160 | cyclohexane | 62 | C ₂₀ H ₂₉ F ₂ N ₂ O ₂ |
| MC1140 | S | H | H | MeSMe | H | H | H | H | H | 117.5-118 | n-hexane | 64 | C ₁₉ H ₂₇ N ₂ O ₂ |

*All compounds were analyzed for C, H, N, S, and, when required, Cl and F; analytical results were within ±0.4% of theoretical values.

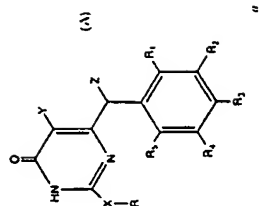


Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds.

| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | CC ₅₀ ^a | [μM] EC ₅₀ ^a | SI ^d |
|---------|---|----|----|----------------------------|-----------------|-----------------|-----------------|----------------|----------------|-------------------------------|---------------------------------------|-----------------|
| MC 507 | O | H | H | 2,5-Me ₂ -c-hex | H | H | H | H | H | 143 | 3.5 | 40 |
| MC 508 | O | H | H | 4,5-Me ₂ -c-hex | H | H | H | H | H | 58 | 6.4 | 9 |
| MC 512 | O | H | H | 3,5-Me ₂ -c-hex | H | H | H | H | H | >200 | 30 | >6.7 |
| MC 531 | O | Me | H | 2,5-Me ₂ -c-hex | H | H | H | H | H | 138 | 3.5 | 39 |
| MC 1114 | O | H | H | sec-but | F | H | H | H | F | 130 | 25 | 52 |
| MC 1103 | O | H | H | c-pent | F | H | H | H | F | >200 | 20 | >10 |
| MC 843 | S | H | H | benzoyloxymethyl | H | H | H | H | H | >200 | 45 | >4 |
| MC 796 | S | H | Ph | sec-but | H | H | H | H | H | 61 | >61 | - |
| MC 890 | S | H | Me | iso-prop | H | H | H | H | H | >200 | .9 | >222 |
| MC 892 | S | H | Me | c-pent | H | H | H | H | H | 159 | .6 | 333 |
| MC 898 | S | H | Me | c-hex | H | H | H | H | H | 149 | .6 | 248 |
| MC 899 | S | H | Et | iso-prop | H | H | H | H | H | 200 | .8 | 250 |
| MC 900 | S | H | Et | c-pent | H | H | H | H | H | >200 | 1.0 | >200 |
| MC 903 | S | H | Et | c-hex | H | H | H | H | H | >200 | 1.3 | >154 |
| MC 806 | S | H | H | sec-but | Me | H | H | H | H | >200 | 1.8 | >111 |
| MC 842 | S | H | H | c-pent | Me | H | H | H | H | >200 | 3.4 | >59 |
| MC 809 | S | H | H | sec-but | H | H | Me | H | H | 200 | 0.6 | 333.3 |
| MC 817 | S | H | H | sec-but | NO ₂ | H | H | H | H | >200 | 0.25 | >800 |
| MC 897 | S | H | H | sec-but | H | NO ₂ | H | H | H | 157 | 0.40 | 392 |
| MC 863 | S | H | H | sec-but | H | H | NO ₂ | H | H | 151 | 1.5 | 101 |
| MC 854 | S | H | H | sec-but | Cl | H | H | H | H | 200 | 1 | 200 |
| MC 857 | S | H | H | sec-but | H | Cl | H | H | H | 116 | 2 | 58 |
| MC 859 | S | H | H | sec-but | H | H | Cl | H | H | 120 | 5 | 24 |
| MC 880 | S | H | H | sec-but | F | H | H | H | H | 200 | 0.26 | 769 |
| MC 884 | S | H | H | sec-but | H | F | H | H | H | >200 | 0.7 | >286 |
| MC 889 | S | H | H | sec-but | H | H | F | H | H | >200 | 8.7 | 23 |
| MC 825 | S | H | H | sec-but | NH ₂ | H | H | H | H | >200 | 21.2 | >9 |
| MC 960 | S | H | H | sec-but | H | H | NH ₂ | H | H | >200 | 23 | >8 |

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Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | CC ₅₀ ^a [μM] | EC ₅₀ ^b [μM] | SI ^d |
|---------|---|---|----|----------|-----------------|----------------|-----------------|----------------|----------------|---------------------------------------|---------------------------------------|-----------------|
| MC 868 | S | H | H | sec-but | CF ₃ | H | H | H | H | >200 | 32 | 6.2 |
| MC 959 | S | H | H | sec-but | H | H | CF ₃ | H | H | 200 | 25 | 8 |
| MC 952 | S | H | H | sec-but | OMe | H | H | H | H | >200 | 1.96 | >208 |
| MC 957 | S | H | H | sec-but | H | OMe | H | H | H | >200 | 1.2 | >166 |
| MC 964 | S | H | H | sec-but | H | H | H | H | H | 147 | 14 | 10.5 |
| MC 1041 | S | H | H | sec-but | H | F | H | F | H | >200 | 1.4 | >143 |
| MC 1042 | S | H | H | sec-but | H | Me | H | Me | H | 133 | 0.6 | 222 |
| MC 877 | S | H | H | Me | Cl | H | H | H | Cl | >200 | 3.2 | >62 |
| MC 878 | S | H | H | iso-prop | Cl | H | H | H | Cl | >200 | 1.9 | >105 |
| MC 886 | S | H | H | n-but | Cl | H | H | H | Cl | >200 | 0.44 | >454 |
| MC 885 | S | H | H | iso-but | Cl | H | H | H | Cl | >200 | 0.45 | >444 |
| MC 815 | S | H | H | sec-but | Cl | H | H | H | Cl | >200 | 0.14 | >1,428 |
| MC 888 | S | H | H | c-pent | Cl | H | H | H | Cl | >200 | 0.4 | >500 |
| MC 891 | S | H | H | c-hex | Cl | H | H | H | Cl | >200 | 0.6 | >333 |
| MC 871 | S | H | H | Me | F | H | H | H | F | 200 | 0.81 | 247 |
| MC 860 | S | H | H | iso-prop | F | H | H | H | F | >200 | 0.2 | >1,000 |
| MC 872 | S | H | H | n-but | F | H | H | H | F | 162 | 0.18 | 900 |
| MC 866 | S | H | H | iso-but | F | H | H | H | F | 182 | 0.14 | 1,300 |
| MC 848 | S | H | H | sec-but | F | H | H | H | F | 200 | 0.04 | 5,000 |
| MC 867 | S | H | H | c-pent | F | H | H | H | F | >200 | 0.08 | >2,500 |
| MC 870 | S | H | H | c-hex | F | H | H | H | F | 200 | 0.08 | 2,500 |
| MC 1001 | S | H | Me | iso-prop | Cl | H | H | H | Cl | 117 | 1.2 | 97.5 |
| MC 996 | S | H | Me | c-pent | Cl | H | H | H | Cl | 78.3 | 1.0 | 78.3 |
| MC 1016 | S | H | Me | c-hex | Cl | H | H | H | Cl | >200 | 2.9 | >69 |
| MC 1000 | S | H | Et | iso-prop | Cl | H | H | H | Cl | >200 | 0.4 | >500 |
| MC 1002 | S | H | Et | c-pent | Cl | H | H | H | Cl | 23.4 | 1.0 | 23.4 |
| MC 1003 | S | H | Et | c-hex | Cl | H | H | H | Cl | >200 | 3.6 | >55.5 |
| MC 1007 | S | H | Me | iso-prop | F | H | H | H | F | 167 | 0.05 | 3,340 |
| MC 1044 | S | H | Me | iso-but | F | H | H | H | F | >200 | 0.05 | >4,000 |
| MC 1045 | S | H | Me | n-but | F | H | H | H | F | >200 | 0.07 | 2,857 |
| MC 1110 | S | H | Me | sec-but | F | H | H | H | F | >200 | 0.03 | >6,666 |
| MC 1008 | S | H | Me | c-pent | F | H | H | H | F | >200 | 0.03 | >6,666 |
| MC 1013 | S | H | Me | c-hex | F | H | H | H | F | >200 | 0.16 | >1,250 |
| MC 1005 | S | H | Et | iso-prop | F | H | H | H | F | 70 | 0.08 | 875 |
| MC 1016 | S | H | Et | c-pent | F | H | H | H | F | 200 | 0.15 | 1,333 |

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

| Compd | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | C ₅₀ ^a | [μM] | EC ₅₀ ^b | SI ^d |
|---------|---|----|----|----------|----------------|-----------------|-----------------|----------------|----------------|------------------------------|-------|-------------------------------|-----------------|
| MC 1014 | S | H | Et | c-hex | F | H | H | H | F | 130 | 0.05 | 0.05 | 2,600 |
| MC 971 | S | H | Me | iso-prop | Cl=CH-CH=CH | Cl=CH-CH=CH | H | H | H | 119 | 1.1 | 1.1 | 108 |
| MC 972 | S | H | Me | c-pent | Cl=CH-CH=CH | Cl=CH-CH=CH | H | H | H | 93 | 0.5 | 0.5 | 186 |
| MC 974 | S | H | Me | c-hex | CH=CH-CH=CH | CH=CH-CH=CH | H | H | H | 45 | 0.14 | 0.14 | 321.4 |
| MC 969 | S | H | Et | iso-prop | CH=CH-CH=CH | CH=CH-CH=CH | H | H | H | 50 | 1.5 | 1.5 | 33.3 |
| MC 973 | S | H | Et | c-pent | CH=CH-CH=CH | CH=CH-CH=CH | H | H | H | 51 | 3.0 | 3.0 | 17 |
| MC 975 | S | H | Et | c-hex | CH=CH-CH=CH | CH=CH-CH=CH | H | H | H | 16.9 | 0.18 | 0.18 | 94 |
| MC 844 | S | Me | H | sec-but | Me | H | H | H | H | >200 | 1.7 | 1.7 | >118 |
| MC 845 | S | Me | H | sec-but | H | H | Me | H | H | 26 | 0.8 | 0.8 | 32 |
| MC 925 | S | Me | H | sec-but | H | NO ₂ | H | H | H | >200 | 0.35 | 0.35 | >571 |
| MC 924 | S | Me | H | sec-but | H | H | NO ₂ | H | H | >200 | 2 | 2 | >100 |
| MC 909 | S | Me | H | sec-but | Cl | H | H | H | H | >200 | 0.27 | 0.27 | >741 |
| MC 910 | S | Me | H | sec-but | H | Cl | H | H | H | >200 | 0.96 | 0.96 | >208 |
| MC 911 | S | Me | H | sec-but | H | H | Cl | H | H | >200 | 9.5 | 9.5 | 20 |
| MC 913 | S | Me | H | sec-but | F | H | H | H | H | 140 | 0.41 | 0.41 | 341 |
| MC 918 | S | Me | H | sec-but | H | F | H | H | H | >200 | 1.2 | 1.2 | >166 |
| MC 919 | S | Me | H | sec-but | H | H | H | H | H | 105 | 1.1 | 1.1 | 9.5 |
| MC 912 | S | Me | H | Me | Cl | H | H | H | Cl | >200 | 3.2 | 3.2 | >62 |
| MC 914 | S | Me | H | iso-prop | Cl | H | H | H | Cl | >200 | 1.3 | 1.3 | >154 |
| MC 920 | S | Me | H | n-but | Cl | H | H | H | Cl | >200 ^c | 1.17 | 1.17 | >171 |
| MC 916 | S | Me | H | iso-but | Cl | H | H | H | Cl | >200 | 1.2 | 1.2 | >166 |
| MC 850 | S | Me | H | sec-but | Cl | H | H | H | Cl | >200 | 0.05 | 0.05 | >4,000 |
| MC 915 | S | Me | H | c-pent | Cl | H | H | H | Cl | >200 | 1.8 | 1.8 | >111 |
| MC 917 | S | Me | H | c-hex | Cl | H | H | H | Cl | >200 | 22 | 22 | >9 |
| MC 869 | S | Me | H | Me | F | H | H | H | F | 200 | 0.19 | 0.19 | 1,053 |
| MC 881 | S | Me | H | iso-prop | F | H | H | H | F | >200 | 0.05 | 0.05 | >4,000 |
| MC 905 | S | Me | H | n-but | F | H | H | H | F | >200 | 0.08 | 0.08 | >2,500 |
| MC 921 | S | Me | H | iso-but | F | H | H | H | F | 64 | 0.1 | 0.1 | 640 |
| MC 849 | S | Me | H | sec-but | F | H | H | H | F | 80 | 0.001 | 0.001 | 8,000 |
| MC 922 | S | Me | H | c-pent | F | H | H | H | F | >200 | 0.08 | 0.08 | >2,500 |
| MC 923 | S | Me | H | c-hex | F | H | H | H | F | >200 | 0.09 | 0.09 | >2,222 |
| MC 1060 | S | Me | Me | Me | F | H | H | H | F | >200 | 0.04 | 0.04 | >5,000 |
| MC 1109 | S | Me | Me | sec-but | F | H | H | H | F | 200 | 0.03 | 0.03 | 6,666 |
| MC 1047 | S | Me | Me | c-pent | F | H | H | H | F | >200 | 0.009 | 0.009 | >22,222 |
| MC 798 | S | Et | H | sec-but | H | H | H | H | H | >200 | 1.0 | 1.0 | >200 |

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | CC ₅₀ ^a | [μ M] | EC ₅₀ ^c | SI ^d |
|---------|----|----------|----|----------|----------------|----------------|----------------|----------------|----------------|-------------------------------|------------|-------------------------------|-----------------|
| MC 1037 | S | Et | H | iso-prop | F | H | H | H | F | 65 | 0.2 | 0.2 | 326 |
| MC 1038 | S | Et | H | sec-but | F | H | H | H | F | >200 | 0.1 | 0.1 | >2,000 |
| MC 804 | S | Et | H | sec-but | CH=CH-CH=CH | H | H | H | H | >200 | 5.3 | 5.3 | >34 |
| MC 1039 | S | iso-prop | H | iso-prop | F | H | H | H | F | >200 | 0.4 | 0.4 | >500 |
| MC 852 | S | allyl | H | sec-but | H | H | H | H | H | >200 | 3 | 3 | >67 |
| MC 856 | S | n-prop | H | sec-but | H | H | H | H | H | 190 | 12 | 12 | 16 |
| MC 834 | S | n-but | H | sec-but | H | H | H | H | H | >200 | >200 | >200 | - |
| MC 1119 | NH | H | H | ethyl | F | H | H | H | F | >200 | 0.8 | 0.8 | >250 |
| MC 1078 | NH | H | H | n-prop | F | H | H | H | F | 200 | 0.11 | 0.11 | 1,818 |
| MC 979 | NH | H | H | iso-prop | F | H | H | H | F | >200 | 0.38 | 0.38 | >526 |
| MC 980 | NH | H | H | c-prop | F | H | H | H | F | >200 | 3.17 | 3.17 | >63 |
| MC 1077 | NH | H | H | n-but | F | H | H | H | F | 100 | 0.10 | 0.10 | 1,000 |
| MC 945 | NH | H | H | sec-but | F | H | H | H | F | >200 | 0.13 | 0.13 | >1,540 |
| MC 1043 | NH | H | H | McOethyl | F | H | H | H | F | >200 | 0.8 | 0.8 | >250 |
| MC 1022 | NH | H | H | c-pent | F | H | H | H | F | >200 | 0.09 | 0.09 | >2,222 |
| MC 1049 | NH | H | H | c-hex | F | H | H | H | F | 66 | 0.14 | 0.14 | 471 |
| MC 1048 | NH | H | Me | c-pent | F | H | H | H | F | 75 | 0.03 | 0.03 | 2,500 |
| MC 1118 | NH | Me | H | iso-prop | F | H | H | H | F | 190 | 0.03 | 0.03 | 6,333 |
| MC 1130 | NH | Me | H | sec-but | F | H | H | H | F | 200 | 0.07 | 0.07 | 2,857 |
| MC 1050 | NH | Me | H | c-pent | F | H | H | H | F | >200 | 0.02 | 0.02 | >10,000 |
| MC 1105 | NH | Me | H | benzyl | F | H | H | H | F | 50 | 0.50 | 0.50 | 100 |
| MC 1129 | NH | Me | H | c-pent | F | H | H | H | F | 90 | 0.02 | 0.02 | 4,500 |
| MC 1167 | NH | H | H | Mc | F | H | H | H | F | >200 | 1.5 | 1.5 | >133 |
| MC 1168 | NH | Me | H | Mc | F | H | H | H | F | 135 | 0.4 | 0.4 | 335 |
| MC 1186 | NH | Me | H | n-prop | F | H | H | H | F | >200 | 0.02 | 0.02 | >10,000 |
| MC 1185 | NH | Me | H | n-but | F | H | H | H | F | >200 | 0.02 | 0.02 | >10,000 |
| MC 1178 | NH | H | Me | Me | F | H | H | H | F | 106 | 0.11 | 0.11 | 964 |
| MC 1190 | NH | H | Me | n-prop | F | H | H | H | F | 103 | 0.02 | 0.02 | 5,150 |
| MC 1191 | NH | H | Me | iso-prop | F | H | H | H | F | 115 | 0.03 | 0.03 | 3,830 |
| MC 1189 | NH | H | Me | n-but | F | H | H | H | F | 52 | 0.03 | 0.03 | 1,730 |
| MC 1192 | NH | H | Me | sec-but | F | H | H | H | F | 86 | 0.04 | 0.04 | 2,150 |
| MC 1180 | NH | H | Me | c-hex | F | H | H | H | F | 56 | 0.02 | 0.02 | 2,545 |
| MC 1170 | NH | Me | Me | Me | F | H | H | H | F | 200 | 0.03 | 0.03 | >6,666 |
| MC 1187 | NH | Me | Me | n-but | F | H | H | H | F | 83 | 0.01 | 0.01 | 8,300 |
| MC 1181 | NH | Me | Me | c-hex | F | H | H | H | F | 58 | 0.03 | 0.03 | 2,231 |

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

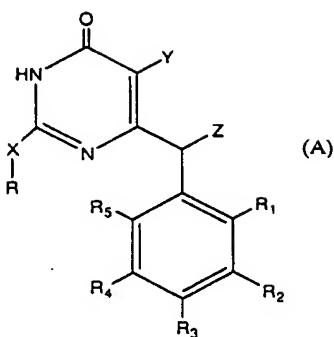
| Compd. | X | Y | Z | R | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | CC ₅₀ ^b | [μ M] | EC ₅₀ ^c | SI ^d |
|----------|---|----------|----|-----------------------|----------------|----------------|----------------|----------------|----------------|-------------------------------|------------|-------------------------------|-----------------|
| MC 1182 | N | H | H | Mc ₂ | F | H | H | H | F | >200 | 0.05 | 0.05 | >4,000 |
| MC 1183 | N | H | H | Mc-piperaz | F | H | H | H | F | >200 | 7.1 | 7.1 | >28 |
| MC 1188 | N | H | H | morph | F | H | H | H | F | >200 | 0.6 | 0.6 | >333 |
| MC 1193 | N | H | H | thiomorph | F | H | H | H | F | >200 | 0.05 | 0.05 | >4,000 |
| MC 1194 | N | H | H | piperid | F | H | H | H | F | >200 | 0.02 | 0.02 | >10,000 |
| MC 1196 | N | H | H | pyrrolid | F | H | H | H | F | >200 | 2.1 | 2.1 | >95 |
| MC 1202 | N | H | H | Et ₂ | F | H | H | H | F | >200 | 0.26 | 0.26 | >769 |
| MC 1204 | N | H | H | (n-prop) ₂ | F | H | H | H | F | >200 | 3.8 | 3.8 | >53 |
| MC 1195 | N | Me | H | Me ₂ | F | H | H | H | F | >200 | 0.02 | 0.02 | >10,000 |
| MC 1203 | N | Me | H | Mc-piperaz | F | H | H | H | F | >200 | 0.36 | 0.36 | >555 |
| MC 1205 | N | Me | H | morph | F | H | H | H | F | >200 | 0.047 | 0.047 | >4,255 |
| MC 1206 | N | Me | H | thiomorph | F | H | H | H | F | >200 | 0.09 | 0.09 | >2,222 |
| MC 1137 | S | Me | Me | iso-prop | F | H | H | H | F | 200 | 0.007 | 0.007 | 28,571 |
| MC 1175 | S | Me | Me | n-but | F | H | H | H | F | 112 | 0.008 | 0.008 | 14,000 |
| MC 1153 | S | Me | Me | iso-but | F | H | H | H | F | >200 | 0.01 | 0.01 | >20,000 |
| MC 1174 | S | Me | Me | c-hex | F | H | H | H | F | >200 | 0.018 | 0.018 | >11,111 |
| MC 1047+ | S | Me | Me | c-pent | F | H | H | H | F | >200 | 0.002 | 0.002 | >100,000 |
| MC 1047- | S | Me | Me | c-pent | F | H | H | H | F | >200 | 0.7 | 0.7 | >286 |
| MC 1161 | S | H | H | McSMc | F | H | H | H | F | >200 | 0.80 | 0.80 | >250 |
| MC 1162 | S | Me | H | McSMc | F | H | H | H | F | 30 | 0.12 | 0.12 | 250 |
| MC 1157 | S | Et | H | McSMc | F | H | H | H | F | 50 | 0.11 | 0.11 | 454 |
| MC 1145 | S | iso-prop | H | McSMc | F | H | H | H | F | 200 | 0.10 | 0.10 | 2,000 |
| MC 1140 | S | H | H | McSMc | H | H | H | H | H | >200 | 20 | 20 | >10 |

^a Data represent mean values of at least two separate experiments.^b Compound dose required to reduce the viability of mock-infected cells by 50%, as determined by the MMT method.^c Compound dose required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity, as determined by the MTT method.^d Selectivity index, CC₅₀/EC₅₀ ratio.

WHAT IS CLAIMED IS:

1. A compound of the formula:

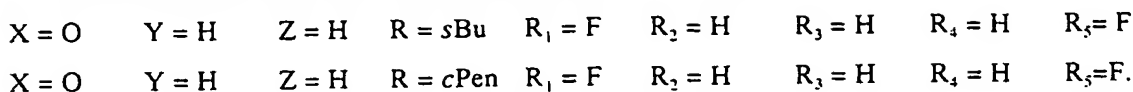
5



wherein:

- X is -O, -CH₂, -CHK (wherein K is -H, -C₁₋₄alkyl, -C₃₋₆cycloalkyl), -S, -NK (wherein K is -H, -C₁₋₄alkyl, -C₃₋₆cycloalkyl), -aryl, -arylalkyl;
- 10 R is -H, -C₁₋₄alkyl (containing one or more of heteroatoms like O, S, N), -C₃₋₆cycloalkyl (containing one or more of heteroatoms like O, S, N), -aryl, arylalkyl, heterocycle;
- Y is -H, -C₁₋₄alkyl, -C₃₋₆cycloalkyl;
- Z is -H, -C₁₋₄alkyl, -C₃₋₆cycloalkyl;
- 15 R₁ is -H, -C₁₋₄alkyl, halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl);
- R₂ is -H, -C₁₋₄alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl);
- 20 R₃ is -H, -C₁₋₄alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, aryl), -SW (wherein W is -H, -CH₃, -aryl);
- R₄ is -H, -C₁₋₄alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl);
- 25 R₅ is -H, -C₁₋₄alkyl, -halogen, -NO₂, -OW (wherein W is -H, -CH₃, -aryl), -SW (wherein W is -H, -CH₃, -aryl), or a pharmaceutically acceptable salt or soluble derivative thereof.

2. A compound having formula A as claimed in claim 1 wherein



5 3. A compound having formula A as claimed in claim 1 wherein

| | | | | | | | | | |
|----|-------|-------|---------------------|---------------------|----------------------------------|--------------------|--------------------|--------------------|---------------------|
| | X = S | Y = H | Z = H | R = sBu | R ₁ = NO ₂ | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = H |
| | X = S | Y = H | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = H |
| | X = S | Y = H | Z = H | R = CH ₃ | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = H | R = iPr | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| 10 | X = S | Y = H | Z = H | R = nBu | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = H | R = iBu | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = H | R = sBu | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = H | R = cPen | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = H | R = cEs | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| 15 | X = S | Y = H | Z = H | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = iBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 20 | X = S | Y = H | Z = H | R = cPen | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = iPr | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = CH ₃ | R = cPen | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = CH ₃ | R = cEs | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| 25 | X = S | Y = H | Z = Et | R = iPr | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = Et | R = cPen | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = Et | R = cEs | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = H | Z = CH ₃ | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = iBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 30 | X = S | Y = H | Z = CH ₃ | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = cPen | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = Et | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 35 | X = S | Y = H | Z = Et | R = cPen | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = Et | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = CH ₃ | R = cEs | -CH=CH-CH=CH | | R ₃ = H | R ₄ = H | R ₅ = H |
| | X = S | Y = H | Z = H | R = sBu | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = H |

| | | | | | | | | | |
|----|-------|---------------------|---------------------|---------------------|---------------------|--------------------|--------------------|--------------------|---------------------|
| | X = S | Y = CH ₃ | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = H |
| | X = S | Y = CH ₃ | Z = H | R = sBu | R ₁ = Cl | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = Cl |
| | X = S | Y = CH ₃ | Z = H | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = H | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 5 | X = S | Y = CH ₃ | Z = H | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = H | R = iBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = H | R = cPen | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = H | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 10 | X = S | Y = CH ₃ | Z = CH ₃ | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = CH ₃ | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = CH ₃ | R = cPe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = Et | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = iPr | Z = H | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 15 | X = S | Y = CH ₃ | Z = CH ₃ | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = CH ₃ | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = CH ₃ | R = iBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = CH ₃ | Z = CH ₃ | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = H | Z = H | R = MeSMe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 20 | X = S | Y = CH ₃ | Z = H | R = MeSMe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = Et | Z = H | R = MeSMe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = S | Y = iPr | Z = H | R = MeSMe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |

4. A compound having formula A as claimed in claim 1 wherein

| | | | | | | | | | |
|----|--------|---------------------|---------------------|-----------|--------------------|--------------------|--------------------|--------------------|--------------------|
| 25 | X = NH | Y = H | Z = H | R = Et | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = nPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = cPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 30 | X = NH | Y = H | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = MeOEt | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = cPe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = cPe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 35 | X = NH | Y = CH ₃ | Z = H | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = H | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = H | R = cPe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = H | R = benz | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |

| | | | | | | | | | |
|----|--------|---------------------|---------------------|-------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | X = NH | Y = CH ₃ | Z = CH ₃ | R = cPe | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = H | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = H | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = H | R = nPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 5 | X = NH | Y = CH ₃ | Z = H | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = nPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = iPr | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 10 | X = NH | Y = H | Z = CH ₃ | R = sBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = H | Z = CH ₃ | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = CH ₃ | R = CH ₃ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = CH ₃ | R = nBu | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = NH | Y = CH ₃ | Z = CH ₃ | R = cEs | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 15 | X = N | Y = H | Z = H | R = (CH ₃) ₂ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = Me-Pip | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = Morph | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = S-morp | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = Piper | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 20 | X = N | Y = H | Z = H | R = Pyrroli | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = Et ₂ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = H | Z = H | R = (nPr) ₂ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = CH ₃ | Z = H | R = (CH ₃) ₂ | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = CH ₃ | Z = H | R = Me-Pip | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| 25 | X = N | Y = CH ₃ | Z = H | R = Morph | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |
| | X = N | Y = CH ₃ | Z = H | R = S-morp | R ₁ = F | R ₂ = H | R ₃ = H | R ₄ = H | R ₅ = F |

5. A pharmaceutically acceptable salt or soluble derivative of a compound of claim 1.

6. A process for the preparation of a compound having formula A as claimed in claim 1

30 wherein X = O, wherein the proper methyl arylacetylalkylacetate is reacted with O-methylisourea in presence of calcium hydroxide; the so obtained 2-O-methyl(5-alkyl)-6-benzyl(substituted)uracils are reacted with the proper potassium alkoxide according to scheme A.

7. A process for the preparation of a compound having formula A as claimed in claim 1

35 wherein X = S, wherein the proper ethyl arylacetylalkylacetate is reacted with thiourea in presence of sodium methoxide; the so obtained 5-alkyl-6-benzyl(substituted)-2-

thiouracils are reacted with methyl iodide or with an alkyl halide in a basic medium according to scheme B.

8. A process for the preparation of the compounds having formula A as claimed in claim 1 wherein X = NK (wherein K is -H, -C₁₋₄alkyl, -C₃₋₆cycloalkyl), wherein the proper S-methyl(5-alkyl)-6-benzyl(substituted)-2-thiouracil is reacted with the proper amine according to scheme C.
9. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof.
10. A pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of a compound claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof, and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS, comprising an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof, and a pharmaceutically acceptable carrier.
12. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof in combination with another anti-HIV agent selected from the group consisting of abacavir, zidovudine, BILA 1906, BILA 2185, BM+51.0836: triazoloisoindolinone derivative, BMS 186,318: aminodiol derivative HIV-1 protease inhibitor, d4API, stavudine, efavirenz, HBY097, HEPT, KNI-272, L-697,593, L-735,524, L-697,661, L-FDDC, L-FDOC, nevirapine, foscarnet, PME A, PMPA, Ro 31-8959, RPI-3121, SC-52151, SC-55389A, TIBO R82150, TIBO 82913, TSAO-m3T, U90152, UC: thiocarboxanilide derivatives, UC-781, UC-82, VB 11,328, amprenavir, XM 323, delaviridine, famciclovir, gancyclovir, penciclovir, indinavir, nelfinavir, ritonavir, saquinavir, DDI, DDC, Delaviridine, β -LddA, β -L-3'-azido-d5FC, carbovir, acyclovir, interferon, stavudine, (3'-azido-2',3'-dideoxy-5-methyl-cytidine), 3'-azido nucleosides, β -D-dioxolane nucleosides such as β -D-dioxolanylguanine (DXG), β -D-dioxolanyl-2,6-diaminopurine (DAPD), and β -D-dioxolanyl-6-chloropurine (ACP), D4T, FTC, 3TC, AZDU, and amprenavir.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05134

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/52 C07D239/56 C07D239/46 C07D239/36 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | <p>ANTONELLO MAI ET AL.: "SYNTHESIS AND ANTI-HIV-1 ACTIVITY OF THIO ANALOGUES OF DIHYDROALKOXYBENZYLLOXYPYRIMIDINES" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 17, 18 August 1995 (1995-08-18), pages 3258-63, XP000578131 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 3258 -page 3262</p> <p style="text-align: center;">— -/-</p> | 1,5,6, 10,11 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

22 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

In . ational Application No
PCT/EP 99/05134

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | CHEMICAL ABSTRACTS, vol. 122, no. 1, 1995 Columbus, Ohio, US; abstract no. 122513c, S. MASSA, A. MAI: "SYNTHESIS AND ANTIVIRAL ACTIVITY OF NEW 3,4-DIHYDRO-2-ALKOXY-6-BENZYL-4-OXOPYRIMID INES" page 23; XP002123508 abstract & ANTIVIRAL CHEM. CHEMOTHER., vol. 6, no. 1, 1995, pages 1-8, ENG | 1,5,6, 10,11 |
| X | WO 91 18887 A (SMITH-KLINE) 12 December 1991 (1991-12-12) page 24; claims | 1,5 |
| X | CHEMICAL ABSTRACTS, vol. 88, no. 21, 1978 Columbus, Ohio, US; abstract no. 152555q, H. FENNER ET AL.: "PYRIMIDO(5,4-B)QUINOLINES" page 604; XP002123509 abstract & ARCH. PHARM., vol. 311, no. 2, 1978, pages 115-125, WEINHEIM | 1 |
| P,X | ANTONELLO MAI ET AL.: "5-ALKYL-2-ALKYLTHIO-6-(2,6-DIHALOPHENYLME THYL)-3,4-DIHYDROPYRIMIDIN-4(3H)-ONES" JOURNAL OF MEDICINAL CHEMISTRY., vol. 42, no. 4, 25 February 1999 (1999-02-25), pages 619-627, XP002123507 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 619 -page 626 | 1,3,5-7, 10,11 |

INTERNATIONAL SEARCH REPORT

...ernational application No.

PCT/EP 99/ 05134

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims No.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 9
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims No.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims No.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims No.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims No.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/05134

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 9118887 A | 12-12-1991 | AU 7971691 A | 31-12-1991 |